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☐	L9	L8 not l1	27
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☐	L7	L5 and (arginine or arg-600 or R600$2 or arg600$3)	114
☐	L6	L5 and KIX	15
☐	L5	L3 and (CBP or CREB adj binding adj protein or CREB-binding adj protein or CBP100) same (polynucleotide or DNA Or RNA or nucle$6 or vector or plasmid)	245
☐	L4	L3 and (polynucleotide or DNA Or RNA or nucle$6 or vector or plasmid)	319
☐	L3	L2 and CREB	327
☐	L2	(CBP or CREB adj binding adj protein or CREB-binding adj protein or CBP100)	2241
☐	L1	Montminy.in. and (CBP or CREB adj binding adj protein)	10

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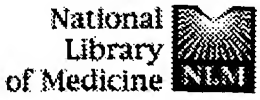

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#42	Search **#40 AND (CREB or cyclic AMP or cAMP or "cyclic adenosine")** Field: **Title/Abstract,** Limits: **Publication Date to 1994**	14:56:35	29
#41	Search **#40 AND (CREB or cyclic AMP or cAMP or "cyclic adenosine")** Field: **Title/Abstract,** Limits: **Publication Date to 1997**	14:55:26	129
#40	Search **#39 not (#1 or #8 or #7)** Field: **Title/Abstract,** Limits: **Publication Date to 1997**	14:54:00	463
#39	Search **CBP or "CREB binding protein" or CREB-binding protein** Field: **Title/Abstract,** Limits: **Publication Date to 1997**	14:53:27	472
#38	Search **(CBP or "CREB binding protein") or CREB-binding protein** Field: **Title/Abstract,** Limits: **Publication Date to 1997**	14:53:19	472
#35	Search **(CBP or "CREB binding protein") AND CREB** Field: **Title/Abstract,** Limits: **Publication Date to 1997**	14:49:48	86
#1	Search **KIX AND CBP**	14:22:29	51
#14	Search **(CBP or CREB binding protein or KIX)** Field: **Title/Abstract,** Limits: **Publication Date to 1994**	14:21:16	495
#17	Search **(CBP or "CREB binding protein") AND CREB** Field: **Title/Abstract,** Limits: **Publication Date to 1994**	11:13:20	6
#16	Search **(CBP or "CREB binding protein")** Field: **Title/Abstract,** Limits: **Publication Date to 1994**	11:13:12	218
#15	Search **(CBP or "CREB binding protein" or KIX)** Field: **Title/Abstract,** Limits: **Publication Date to 1994**	11:12:53	218
#12	Search **(CBP or CREB binding protein) AND (muta* or glutamine or substitution or 600) AND KIX** Field: **Title/Abstract**	10:08:21	19
#11	Search **(CBP or CREB binding protein) AND glutamine AND KIX** Field: **Title/Abstract**	10:08:02	0
#10	Search **CBP AND glutamine AND KIX** Field: **Title/Abstract**	10:07:50	0

#8 Search **CBP AND glutamine** Field: **Title/Abstract**	10:06:45	18
#7 Search **CBP AND glutamine**	10:06:33	21

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STN

FILE 'HOME' ENTERED AT 15:40:07 ON 01 NOV 2004

L8 969 L4 AND(CBP OR CREB (A) BINDING (A) PROTEIN)(P) (BINDING OR FUNCTIONAL) (S) (DOMAIN OR REGION)

'HOME' ENTERED AT 15:40:07 ON 01 NOV 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 15:40:29 ON 01 NOV 2004

L1 6295 S (CBP OR CREB (A) BINDING (A) PROTEIN) AND (CREB OR CAMP)
L2 5827 S (CBP OR CREB (A) BINDING (A) PROTEIN) (S) CREB
L3 0 S L2 AND (CBP OR CREB (A) BINDING (A) PROTEIN)/ABS
L4 2128 S L2 AND (CBP OR CREB (A) BINDING (A) PROTEIN)/TI
L5 52 S L4 AND (ARGININE OR 600) (P) (CBP OR BINDING (A) PROTEIN)
L6 19 DUP REM L5 (33 DUPLICATES REMOVED)
L7 980 S L4 AND (BINDING OR FUNCTIONAL) (S) (DOMAIN OR REGION)
L8 969 S L4 AND(CBP OR CREB (A) BINDING (A) PROTEIN)(P) (BINDING OR
L9 0 S L8 AND @PY<1998
L10 166 S L8 AND PY<1998
L11 47 DUP REM L10 (119 DUPLICATES REMOVED)
L12 46 S L11 NOT L6
L13 244 S L2 AND KIX
L14 64 DUP REM L13 (180 DUPLICATES REMOVED)
L15 56 S L14 NOT (L12 OR L6)
L16 0 S L15 AND PY<1998

(FILE 'HOME' ENTERED AT 15:40:07 ON 01 NOV 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 15:40:29 ON 01 NOV 2004

L1	6295	S (CBP OR CREB (A) BINDING (A) PROTEIN) AND (CREB OR CAMP)
L2	5827	S (CBP OR CREB (A) BINDING (A) PROTEIN) (S) CREB
L3	0	S L2 AND (CBP OR CREB (A) BINDING (A) PROTEIN)/ABS
L4	2128	S L2 AND (CBP OR CREB (A) BINDING (A) PROTEIN)/TI
L5	52	S L4 AND (ARGININE OR 600) (P) (CBP OR BINDING (A) PROTEIN)
L6	19	DUP REM L5 (33 DUPLICATES REMOVED)
L7	980	S L4 AND (BINDING OR FUNCTIONAL) (S) (DOMAIN OR REGION)
L8	969	S L4 AND(CBP OR CREB (A) BINDING (A) PROTEIN)(P) (BINDING OR
L9	0	S L8 AND @PY<1998
L10	166	S L8 AND PY<1998
L11	47	DUP REM L10 (119 DUPLICATES REMOVED)
L12	46	S L11 NOT L6
L13	244	S L2 AND KIX
L14	64	DUP REM L13 (180 DUPLICATES REMOVED)
L15	56	S L14 NOT (L12 OR L6)
L16	0	S L15 AND PY<1998
L17	31	S L2 AND KIX (P) (ARGININE OR 600)
L18	8	DUP REM L17 (23 DUPLICATES REMOVED)

L6 ANSWER 4 OF 19 MEDLINE on STN DUPLICATE 2
AN 2003308172 MEDLINE
DN PubMed ID: 12795599
TI Contribution to stability and folding of a buried polar residue at the CARM1 methylation site of the KIX domain of **CBP**.
AU Wei Yu; Horng Jia-Cherng; Vendel Andrew C; Raleigh Daniel P; Lumb Kevin J
CS Department of Biochemistry and Molecular Biology, Colorado State University, Fort Collins, Colorado 80523-1870, USA.
NC R01 GM54233 (NIGMS)
SO Biochemistry, (2003 Jun 17) 42 (23) 7044-9.
Journal code: 0370623. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200307
ED Entered STN: 20030703
Last Updated on STN: 20030725
Entered Medline: 20030724
AB The transcriptional coactivator and acetyltransferase **CREB Binding Protein** (**CBP**) is comprised of several autonomously folded and functionally independent domains. The KIX domain mediates interactions between **CBP** and numerous transcriptional activators. The folded region of KIX has all the structural features of a globular protein, including three alpha-helices, two short 3(10) helices, and a well-packed hydrophobic core. KIX contains a buried cation-pi interaction between the positively charged guanidinium group of Arg **600** and the aromatic ring of Tyr 640. Arg **600** is a site for regulatory methylation by CARM1/PRMT4, which negates the CREB-binding function of the KIX domain. The role of the Arg **600**-Tyr 640 buried polar interaction in specifying and stabilizing the structure of KIX was investigated by comparing the folding of wild-type KIX with the single point mutants Y640F and R600M. The Y640F mutant disrupts a hydrogen bond involving the Tyr 640 OH and the backbone of V595 but still allows for the cation-pi interaction while the R600M mutant disrupts the cation-pi interaction. Both wild type KIX and Y640F exhibit properties expected of native like, globular proteins such as a single oligomerization state (monomer), cooperative thermal and urea-induced unfolding transitions, and a well-packed core. In contrast, the R600M mutant has properties reminiscent of a molten globule state, including a tendency to aggregate, noncooperative thermal unfolding transition, and a loosely packed core. Thus, the buried cation-pi interaction is critical for specifying the unique cooperatively folded structure of KIX.

L6 ANSWER 7 OF 19 MEDLINE on STN DUPLICATE 5
AN 2003544242 MEDLINE
DN PubMed ID: 14623102
TI Mutational analysis of the KIX domain of **CBP** reveals residues critical for SREBP binding.
AU Liu Ya-Ping; Chang Ching-Wen; Chang Kung-Yao
CS Institute of Biochemistry, National Chung-Hsing University, 250 Kuo-Kung Road, Taichung 402, Taiwan.
SO FEBS letters, (2003 Nov 20) 554 (3) 403-9.
Journal code: 0155157. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200312

ED Entered STN: 20031119
Last Updated on STN: 20031219
Entered Medline: 20031218

AB Structure-based mutagenesis was used to probe the binding surface for the activation domain of sterol-responsive element **binding protein** (SREBP) in the KIX domain of **CREB binding protein**. A set of conserved residues scattering in the alpha2 helix and the extended C-terminal region of alpha 3 helix in the KIX domain including two **arginines** previously characterized as a hot spot for cofactor-mediated methylation was shown to be crucial for SREBP-KIX interaction, and was not essential for phosphorylated KID recognition. Therefore, our results suggest the existence of a SREBP binding site formed by positively charged residues in the C-terminal part of the extended alpha 3 helix of the KIX domain distinct from the previously identified phosphorylated KID binding site.

L6 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:282612 CAPLUS
DN 135:340116
TI Magnitude of the **CREB**-dependent transcriptional response is determined by the strength of the interaction between the kinase-inducible domain of **CREB** and the KIX domain of **CREB-binding protein**
AU Shaywitz, Adam J.; Dove, Simon L.; Kornhauser, Jon M.; Hochschild, Ann; Greenberg, Michael E.
CS Program in Biological and Biomedical Sciences, Harvard Medical School, Children's Hospital, Boston, MA, 02115, USA
SO Molecular and Cellular Biology (2000), 20(24), 9409-9422
CODEN: MCEBD4; ISSN: 0270-7306
PB American Society for Microbiology
DT Journal
LA English

AB The activity of the transcription factor CREB is regulated by extracellular stimuli that result in its phosphorylation at a critical serine residue, Ser133. Phosphorylation of Ser133 is believed to promote **CREB**-dependent transcription by allowing **CREB** to interact with the transcriptional coactivator **CREB-binding protein** (**CBP**). Previous studies have established that the domain encompassing Ser133 on **CREB**, known as the kinase-inducible domain (KID), interacts specifically with a short domain in **CBP** termed the KIX domain and that this interaction depends on the phosphorylation of Ser133. In this study, the authors adapted a recently described Escherichia coli-based two-hybrid system for the examination of phosphorylation-dependent protein-protein interactions, and they used this system to study the kinase-induced interaction between the KID and the KIX domain. The authors identified residues of the KID and the KIX domain that are critical for their interaction as well as two pairs of oppositely charged residues that apparently interact at the KID-KIX interface. The authors then isolated a mutant form of the KIX domain that interacts more tightly with wild-type and mutant forms of the KID than does the wild-type KIX domain. The authors show that in the context of full-length **CBP**, the corresponding amino acid substitution resulted in an enhanced ability of **CBP** to stimulate **CREB**-dependent transcription in mammalian cells. Conversely, an amino acid substitution in the KIX domain that weakens its interaction with the KID resulted in a decreased ability of full-length **CBP** to stimulate **CREB**-dependent transcription. These findings demonstrate that the magnitude of CREB-dependent transcription in mammalian cells depends on the strength of the KID-KIX interaction and suggest that the level of transcription induced by coactivator-dependent transcriptional activators

can be specified by the strength of the activator-coactivator interaction.

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 19 OF 19 MEDLINE on STN DUPLICATE 11
AN 96140437 MEDLINE
DN PubMed ID: 8552098
TI Phosphorylation of **CREB** at Ser-133 induces complex formation with **CREB-binding protein** via a direct mechanism.
AU Parker D; Ferreri K; Nakajima T; LaMorte V J; Evans R; Koerber S C; Hoeger C; Montminy M R
CS Clayton Foundation Laboratories for Peptide Biology, Salk Institute, La Jolla, California 92037, USA.
NC CA54418 (NCI)
GM37828 (NIGMS)
SO Molecular and cellular biology, (1996 Feb) 16 (2) 694-703.
Journal code: 8109087. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199602
ED Entered STN: 19960306
Last Updated on STN: 19960306
Entered Medline: 19960221
AB We have characterized a phosphoserine binding domain in the coactivator **CREB-binding protein** (**CBP**) which interacts with the protein kinase A-phosphorylated, and hence activated, form of the cyclic AMP-responsive factor **CREB**. The CREB binding domain, referred to as KIX, is alpha helical and binds to an unstructured kinase-inducible domain in CREB following phosphorylation of CREB at Ser-133. Phospho-Ser-133 forms direct contacts with residues in KIX, and these contacts are further stabilized by hydrophobic residues in the kinase-inducible domain which flank phospho-Ser-133. Like the src homology 2 (SH2) domains which bind phosphotyrosine-containing peptides, phosphoserine 133 appears to coordinate with a single **arginine** residue (Arg-**600**) in KIX which is conserved in the **CBP** -related protein P300. Since mutagenesis of Arg-**600** to Gln severely reduces **CREB-CBP** complex formation, our results demonstrate that, as in the case of tyrosine kinase pathways, signal transduction through serine/threonine kinase pathways may also require protein interaction motifs which are capable of recognizing phosphorylated amino acids.

(CBP OR CREB (A) BINDING (A) PROTEIN)

L12 ANSWER 1 OF 46 MEDLINE on STN
AN 1998074795 MEDLINE
DN PubMed ID: 9413984
TI Solution structure of the KIX domain of **CBP** bound to the transactivation domain of **CREB**: a model for activator:coactivator interactions.
AU Radhakrishnan I; Perez-Alvarado G C; Parker D; Dyson H J; Montminy M R; Wright P E
CS Department of Molecular Biology, and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, California 92037, USA.
SO Cell, **(1997 Dec 12)** 91 (6) 741-52.
Journal code: 0413066. ISSN: 0092-8674.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS PDB-1KDX
EM 199801
ED Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980113
AB The nuclear factor **CREB** activates transcription of target genes in part through direct interactions with the KIX domain of the coactivator **CBP** in a phosphorylation-dependent manner. The solution structure of the complex formed by the phosphorylated kinase-inducible **domain** (pKID) of CREB with KIX reveals that pKID undergoes a coil-->helix folding transition upon **binding** to KIX, forming two alpha helices. The amphipathic helix alphaB of pKID interacts with a hydrophobic groove defined by helices alpha1 and alpha3 of KIX. The other pKID helix, alphaA, contacts a different face of the alpha3 helix. The phosphate group of the critical phosphoserine residue of pKID forms a hydrogen bond to the side chain of Tyr-658 of KIX. The structure provides a model for interactions between other transactivation domains and their targets.

L12 ANSWER 6 OF 46 MEDLINE on STN
AN 97431612 MEDLINE
DN PubMed ID: 9287117
TI Trans-activation by the Drosophila myb gene product requires a Drosophila homologue of **CBP**.
AU Hou D X; Akimaru H; Ishii S
CS Laboratory of Molecular Genetics, Tsukuba Life Science Center, RIKEN, Ibaraki, Japan.
SO FEBS letters, **(1997 Aug 11)** 413 (1) 60-4.
Journal code: 0155157. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 19971224
Last Updated on STN: 20000303
Entered Medline: 19971030
AB Attempts to demonstrate trans-activation activity by the Drosophila myb gene product (D-Myb) have been unsuccessful so far. We demonstrate that co-transfection of Schneider cells with a plasmid expressing the Drosophila homologue of transcriptional co-activator **CBP** (dCBP) results in transactivation by D-Myb. Using this assay system, the **functional domains** of D-Myb were analyzed. Two

domains located in the N-proximal **region**, one of which is required for DNA **binding** and the other for dCBP **binding**, are both necessary and sufficient for trans-activation. In this respect, D-Myb is similar to c-Myb and A-Myb, but different from mammalian B-Myb. These results shed light on how the myb gene diverged during the course of evolution.

L12 ANSWER 15 OF 46 MEDLINE on STN
AN 97122333 MEDLINE
DN PubMed ID: 8967953
TI The **CBP** co-activator is a histone acetyltransferase.
AU Bannister A J; Kouzarides T
CS Wellcome/CRC Institute, Cambridge, UK.
SO Nature, **(1996 Dec 19-26)** 384 (6610) 641-3.
Journal code: 0410462. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199701
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970109
AB The **CBP** protein acts as a transcriptional adaptor for many different transcription factors by directly contacting DNA-bound activators. One mechanism by which **CBP** is thought to stimulate transcription is by recruiting the histone acetyltransferase (HAT) P/CAF to the promoter. Here we show that **CBP** has intrinsic HAT activity. The HAT **domain** of **CBP** is adjacent to the **binding** site for the transcriptional activator E1A. Although E1A displaces P/CAF from **CBP**, it does not disrupt the **CBP** -associated HAT activity. Thus E1A carries HAT activity when complexed with **CBP**. Targeting **CBP**-associated HAT activity to specific promoters may therefore be a mechanism by which E1A acts as a transcriptional activator.

L12 ANSWER 16 OF 46 MEDLINE on STN
AN 97098492 MEDLINE
DN PubMed ID: 8943032
TI A positive genetic selection for disrupting protein-protein interactions: identification of **CREB** mutations that prevent association with the coactivator **CBP**.
AU Shih H M; Goldman P S; DeMaggio A J; Hollenberg S M; Goodman R H; Hoekstra M F
CS Vollum Institute, Oregon Health Sciences University, Portland 97201, USA.
NC DK09396 (NIDDK)
DK45423 (NIDDK)
SO Proceedings of the National Academy of Sciences of the United States of America, **(1996 Nov 26)** 93 (24) 13896-901.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199701
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970116
AB The Escherichia coli tet-repressor (TetR) operator system was used to develop a variation of the yeast two-hybrid assay in which disruptions of

protein-protein interactions can be identified by a positive selection. This assay, designated the "split-hybrid system," contains a two-component reporter. The first component contains LexA binding sites upstream of the TetR gene and the second contains TetR operator binding sites upstream of HIS3. Interaction of one protein fused to the LexA DNA **binding domain** with a second protein fused to the VP16 activation **domain** results in TetR expression. TetR subsequently binds to the tet operators, blocking the expression of HIS3 and preventing yeast growth in media lacking histidine. The utility of the split-hybrid system was analyzed by examining the phosphorylation-dependent interaction of **CREB** and its coactivator **CREB binding protein** (**CBP**). **CREB** and **CBP** associate through an interaction that depends upon **CREB** phosphorylation at Ser-133. Mutation of this phosphorylation site prevents yeast growth in the standard two-hybrid assay but allows growth in the split-hybrid strains. The split-hybrid system was used to identify other **CREB** mutations that disrupt its association with **CBP**. These mutations localized around the site of **CREB** phosphorylation, indicating that only a small portion of the **CREB** activation domain is required for **CBP** interaction. The yeast split-hybrid system should be useful in identifying mutations, proteins, peptides, and drugs that disrupt protein-protein interactions.

L12 ANSWER 18 OF 46 MEDLINE on STN
AN 97067026 MEDLINE
DN PubMed ID: 8910428
TI **CREB-binding protein** activates transcription through multiple **domains**.
AU Swope D L; Mueller C L; Chrivia J C
CS Department of Pharmacological and Physiological Sciences, Saint Louis University School of Medicine, St. Louis, Missouri 63104, USA.
SO Journal of biological chemistry, **(1996 Nov 8)** 271 (45) 28138-45.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199612
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961230
AB **CREB-binding protein** (**CBP**) functions as a coactivator molecule for a number of transcription factors including **CREB**, c-Fos, c-Jun, c-Myb, and several nuclear receptors. Although **binding** sites for these factors within **CBP** have been identified, the **regions** of **CBP** responsible for transcriptional activation are unknown. In this report, we show that the N-terminal half of **CBP** is sufficient for activation of **CREB**-mediated transcription and that this region contains a strong transcriptional activation domain (TAD). Both deletion of this TAD or sequestering of factors that the TAD binds using a squelching assay were found to greatly decrease the ability of **CBP** to activate **CREB**-mediated transcription. In vivo studies by others have shown that p300/**CBP** associates with TBP; using an in vitro approach, we show the N-terminal TAD binds TBP. We also examined the ability of the C terminus of **CBP** to activate transcription using GAL-**CBP** chimeras. With this approach, we identified two C-terminal TADs located adjacent to the c-Fos binding site. In previous studies, cAMP-dependent protein kinase A (PKA) increased the transcriptional activity of a GAL full-length **CBP** chimera in F9

cells, and of the C terminus in PC-12 cells. Here, we demonstrate that PKA also increased the ability of the N-terminal TADs of **CBP** to activate transcription in PC-12 but not F9 or COS-7 cells, suggesting that this PKA-responsiveness is cell type-specific.

L12 ANSWER 21 OF 46 MEDLINE on STN
AN 96279308 MEDLINE
DN PubMed ID: 8663603
TI Identification and characterization of a novel transcriptional activation **domain** in the **CREB-binding protein**.
AU Bisotto S; Minorgan S; Rehfuss R P
CS Laboratory of Molecular Endocrinology, Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada H3A 1A1.
SO Journal of biological chemistry, **(1996 Jul 26)** 271 (30) 17746-50.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199609
ED Entered STN: 19960912
Last Updated on STN: 19960912
Entered Medline: 19960903
AB The **CREB-binding protein** (**CBP**) plays a central role in the regulation of gene expression by several different second messenger pathways including serum growth factors, cAMP and phorbol esters. **CBP** specifically binds to the phosphorylated forms of **CREB** and c-Jun and is thought to activate transcription through a C-terminal activation domain. In this report, we demonstrate that the C terminus of **CBP** is dispensable for its ability to stimulate phospho-**CREB** activity, and, further, that the deletion of this domain produces highly active, mutant forms of **CBP**. The novel N-terminal activation identified by this deletional analysis consists of the first 714 amino acids of CBP and is sufficient for high levels of transcriptional activity. This domain is also capable of stimulating the activity of a second cAMP-regulated factor, ATF-1. Surprisingly, ATF-1 activity is not significantly stimulated by full-length CBP suggesting that the C-terminal domain of CBP may also serve to regulate ATF-1/CBP activity. Additionally, the demonstration that one of our hyperactive **CBP** mutants is able to activate a nonphosphorylatable mutant of **CREB** (M1 **CREB**) provides the first evidence that **CBP** may play a role in regulating the basal transcriptional activity of **CREB**.

L12 ANSWER 24 OF 46 MEDLINE on STN
AN 96201529 MEDLINE
DN PubMed ID: 8616895
TI A **CBP** integrator complex mediates transcriptional activation and AP-1 inhibition by nuclear receptors.
AU Kamei Y; Xu L; Heinzel T; Torchia J; Kurokawa R; Gloss B; Lin S C; Heyman R A; Rose D W; Glass C K; Rosenfeld M G
CS Howard Hughes Medical Institute, School of Medicine, University of California, San Diego, La Jolla, 92093-0648, USA.
SO Cell, **(1996 May 3)** 85 (3) 403-14.
Journal code: 0413066. ISSN: 0092-8674.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 199606
ED Entered STN: 19960620
Last Updated on STN: 19960620
Entered Medline: 19960613
AB Nuclear receptors regulate gene expression by direct activation of target genes and inhibition of AP-1. Here we report that, unexpectedly, activation by nuclear receptors requires the actions of **CREB-binding protein** (**CBP**) and that inhibition of AP-1 activity is the apparent result of competition for limiting amounts of **CBP**/p300 in cells. Utilizing distinct **domains**, **CBP** directly interacts with the ligand-**binding domain** of multiple nuclear receptors and with the p160 nuclear receptor coactivators, which upon cloning have proven to be variants of the SRC-1 protein. Because **CBP** represents a common factor, required in addition to distinct coactivators for function of nuclear receptors, **CREB**, and AP-1, we suggest that **CBP**/p300 serves as an integrator of multiple signal transduction pathways within the nucleus.

L12 ANSWER 25 OF 46 MEDLINE on STN
AN 96186817 MEDLINE
DN PubMed ID: 8602268
TI Control of cAMP-regulated enhancers by the viral transactivator Tax through **CREB** and the co-activator **CBP**.
AU Kwok R P; Laurance M E; Lundblad J R; Goldman P S; Shih H; Connor L M; Marriott S J; Goodman R H
CS Vollum Institute, Oregon Health Sciences University, Portland 97201 USA.
SO Nature, **(1996 Apr 18)** 380 (6575) 642-6.
Journal code: 0410462. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199605
ED Entered STN: 19960517
Last Updated on STN: 19970203
Entered Medline: 19960508
AB The Tax protein of human T-lymphotropic virus (HTLV)-1 activates expression of the HTLV-1 long terminal repeat through a DNA element that resembles the cellular cyclic AMP-regulated enhancer (CRE). Tax contains a transcriptional activation **domain**, but its ability to activate gene expression depends on interactions with cellular CRE-**binding** proteins such as CREB. Whether Tax can activate the expression of cellular CRE-containing genes has been controversial. Here we show that Tax can activate both the HTLV-1 and consensus cellular CREs, and propose that this activation may occur through mechanisms that are differentially dependent on CREB phosphorylation. Tax not only increases the binding of **CREB** to the viral CRE but also recruits the transcriptional co-activator **CBP** in a manner independent of **CREB** phosphorylation. In contrast, association of Tax with the cellular CRE occurs through **CBP** which, in turn, is recruited only in the presence of phosphorylated **CREB**.

L12 ANSWER 30 OF 46 MEDLINE on STN
AN 95221348 MEDLINE
DN PubMed ID: 7706240
TI An inactivating point mutation demonstrates that interaction of cAMP response element binding protein (**CREB**) with the **CREB binding protein** is not sufficient for transcriptional

activation.
AU Sun P; Maurer R A
CS Department of Cell Biology and Anatomy, Oregon Health Sciences University, Portland 97201, USA.
SO Journal of biological chemistry, **(1995 Mar 31)** 270 (13) 7041-4.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199505
ED Entered STN: 19950518
Last Updated on STN: 19980206
Entered Medline: 19950510
AB The cAMP response element binding protein (CREB) mediates transcriptional activation in response to the cAMP signaling pathway. Several recent studies have suggested that phosphorylation-dependent interaction of **CREB** with a co-activator designated **CREB binding protein** (**CBP**) is a crucial step in mediating transcriptional responses to cAMP. In the present study we have determined that replacement of Ser142 of CREB with Asp greatly decreases the ability of the cAMP-dependent protein kinase to activate CREB. As Ser142 is located within the **region** of **CREB** that interacts with **CBP**, it seemed quite likely that mutations at this site might interfere with **binding** to **CBP**. However, both in vitro and in vivo protein-protein interaction assays revealed that replacement of Ser142 with Asp does not interfere with the binding of **CREB** to **CBP**. These studies argue strongly that although the binding of **CREB** to **CBP** is necessary, it is not sufficient for transcriptional responses to cAMP.

L12 ANSWER 32 OF 46 MEDLINE on STN
AN 94301408 MEDLINE
DN PubMed ID: 7913207
TI Nuclear protein **CBP** is a coactivator for the transcription factor **CREB**.
CM Comment in: Nature. 1994 Jul 21;370(6486):177-8. PubMed ID: 8028657
AU Kwok R P; Lundblad J R; Chrivia J C; Richards J P; Bachinger H P; Brennan R G; Roberts S G; Green M R; Goodman R H
CS Vollum Institute, Oregon Health Sciences University, Portland 97201.
SO Nature, **(1994 Jul 21)** 370 (6486) 223-6.
Journal code: 0410462. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199408
ED Entered STN: 19940818
Last Updated on STN: 19970203
Entered Medline: 19940805
AB The transcription factor CREB binds to a DNA element known as the cAMP-regulated enhancer (CRE). CREB is activated through phosphorylation by protein kinase A (PKA), but precisely how phosphorylation stimulates CREB function is unknown. One model is that phosphorylation may allow the recruitment of coactivators which then interact with basal transcription factors. We have previously identified a nuclear protein of M(r)265K, **CBP**, that binds specifically to the PKA-phosphorylated form of **CREB**. We have used fluorescence anisotropy measurements to define the equilibrium **binding** parameters of the phosphoCREB: **CBP** interaction and report here that **CBP** can activate

transcription through a **region** in its carboxy terminus. The activation domain of **CBP** interacts with the basal transcription factor TFIIB through a domain that is conserved in the yeast coactivator ADA-1 (reference 8). Consistent with its role as a coactivator, **CBP** augments the activity of phosphorylated **CREB** to activate transcription of cAMP-responsive genes.

L12 ANSWER 33 OF 46 MEDLINE on STN
AN 94019866 MEDLINE
DN PubMed ID: 8413673
TI Phosphorylated **CREB** binds specifically to the nuclear protein **CBP**.
AU Chrivia J C; Kwok R P; Lamb N; Hagiwara M; Montminy M R; Goodman R H
CS Vollum Institute, Oregon Health Sciences University, Portland 97201.
SO Nature, **(1993 Oct 28)** 365 (6449) 855-9.
Journal code: 0410462. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199311
ED Entered STN: 19940117
Last Updated on STN: 19950206
Entered Medline: 19931124
AB Cyclic AMP-regulated gene expression frequently involves a DNA element known as the cAMP-regulated enhancer (CRE). Many transcription factors bind to this element, including the protein CREB, which is activated as a result of phosphorylation by protein kinase A. This modification stimulates interaction with one or more of the general transcription factors or, alternatively, allows recruitment of a co-activator. Here we report that **CREB** phosphorylated by protein kinase A binds specifically to a nuclear protein of M(r) 265K which we term **CBP** (for **CREB-binding protein**). Fusion of a heterologous DNA-**binding domain** to the amino terminus of **CBP** enables the chimaeric protein to function as a protein kinase A-regulated transcriptional activator. We propose that **CBP** may participate in cAMP-regulated gene expression by interacting with the activated pho

L12 ANSWER 37 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:550505 CAPLUS
DN 121:150505
TI E1A-associated p300 and **CREB**-associated **CBP** belong to a conserved family of coactivators
AU Arany, Zoltan; Sellers, William R.; Livingston, David M.; Eckner, Richard
CS Dana-Farber Cancer Institute, Boston, MA, 02115, USA
SO Cell (Cambridge, MA, United States) (**1994**), 77(6), 799-800
CODEN: CELLB5; ISSN: 0092-8674
DT Journal
LA English
AB Amino acid sequence comparison of the E1A-associated protein p300 and **CREB**-associated protein **CBP** showed numerous regions of near identity. These 2 proteins, although from different species, were 85% identical and more than 95% homologous over a central colinear segment of 800 amino acids. Based on the high degree of conservation in the E1A-**binding region**, the authors proposed that **CBP** may bind E1A and the E1A-associated p300 may be more than one protein.

L12 ANSWER 41 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 97153065 EMBASE
DN 1997153065
TI Construction of a 1.2-Mb contig surrounding, and molecular analysis of, the human **CREB-binding protein** (**CBP** /CREBBP) gene on chromosome 16p13.3.
AU Giles R.H.; Petrij F.; Dauwerse H.G.; Den Hollander A.I.; Lushnikova T.; Van Ommen G.-J.B.; Goodman R.H.; Deaven L.L.; Doggett N.A.; Peters D.J.M.; Breuning M.H.
CS M.H. Breuning, Sylvius Laboratories, Department of Human Genetics, Leiden University, Wassenaarseweg 72, 2333 AL Leiden, Netherlands
SO Genomics, (1997) 42/1 (96-114).
Refs: 87
ISSN: 0888-7543 CODEN: GNMCEP
CY United States
DT Journal; Article
FS 022 Human Genetics
LA English
SL English
AB In the interest of cloning and analyzing the genes responsible for two very different diseases, the Rubinstein-Taybi syndrome (RTS) and acute myeloid leukemia (AML) associated with the somatic translocation t(8;16)(p11;p13.3), we constructed a high-resolution restriction map of contiguous cosmids (contig) covering 1.2 Mb of chromosome 16p13.3. By fluorescence in situ hybridization and Southern blot analysis, we assigned all tested RTS and t(8;16) translocation breakpoints to a 100-kb **region**. We have previously reported exact physical locations of these 16p breakpoints, which all disrupt one gene we mapped to this interval: the **CREB-binding protein** (**CBP** or CREBBP) gene. Intriguingly, mutations in the **CBP** gene are responsible for RTS as well as the t(8;16).associated AML. **CBP** functions as an integrator in the assembly of various multiprotein regulatory complexes and is thus necessary for transcription in a broad range of transduction pathways. We report here the cloning, physical mapping, characterization, and full cDNA nucleotide sequence of the human **CBP** gene.

FILE 'HOME' ENTERED AT 15:40:07 ON 01 NOV 2004

L8 969 L4 AND(CBP OR CREB (A) BINDING (A) PROTEIN)(P) (BINDING OR FUNCTIONAL) (S) (DOMAIN OR REGION)

'HOME' ENTERED AT 15:40:07 ON 01 NOV 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 15:40:29 ON 01 NOV 2004

L1 6295 S (CBP OR CREB (A) BINDING (A) PROTEIN) AND (CREB OR CAMP)
L2 5827 S (CBP OR CREB (A) BINDING (A) PROTEIN) (S) CREB
L3 0 S L2 AND (CBP OR CREB (A) BINDING (A) PROTEIN)/ABS
L4 2128 S L2 AND (CBP OR CREB (A) BINDING (A) PROTEIN)/TI
L5 52 S L4 AND (ARGININE OR 600) (P) (CBP OR BINDING (A) PROTEIN)
L6 19 DUP REM L5 (33 DUPLICATES REMOVED)
L7 980 S L4 AND (BINDING OR FUNCTIONAL) (S) (DOMAIN OR REGION)
L8 969 S L4 AND(CBP OR CREB (A) BINDING (A) PROTEIN)(P) (BINDING OR
L9 0 S L8 AND @PY<1998
L10 166 S L8 AND PY<1998
L11 47 DUP REM L10 (119 DUPLICATES REMOVED)
L12 46 S L11 NOT L6
L13 244 S L2 AND KIX
L14 64 DUP REM L13 (180 DUPLICATES REMOVED)
L15 56 S L14 NOT (L12 OR L6)
L16 0 S L15 AND PY<1998

L18 ANSWER 1 OF 8 MEDLINE on STN DUPLICATE 1
AN 2003308172 MEDLINE
DN PubMed ID: 12795599
TI Contribution to stability and folding of a buried polar residue at the CARM1 methylation site of the KIX domain of CBP.
AU Wei Yu; Horng Jia-Cherng; Vendel Andrew C; Raleigh Daniel P; Lumb Kevin J
CS Department of Biochemistry and Molecular Biology, Colorado State University, Fort Collins, Colorado 80523-1870, USA.
NC R01 GM54233 (NIGMS)
SO Biochemistry, (2003 Jun 17) 42 (23) 7044-9.
Journal code: 0370623. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200307
ED Entered STN: 20030703
Last Updated on STN: 20030725
Entered Medline: 20030724
AB The transcriptional coactivator and acetyltransferase **CREB Binding Protein** (**CBP**) is comprised of several autonomously folded and functionally independent domains. The **KIX** domain mediates interactions between CBP and numerous transcriptional activators. The folded region of **KIX** has all the structural features of a globular protein, including three alpha-helices, two short 3(10) helices, and a well-packed hydrophobic core. **KIX** contains a buried cation-pi interaction between the positively charged guanidinium group of Arg **600** and the aromatic ring of Tyr 640. Arg **600** is a site for regulatory methylation by CARM1/PRMT4, which negates the CREB-binding function of the **KIX** domain. The role of the Arg **600**-Tyr 640 buried polar interaction in specifying and stabilizing the structure of **KIX** was investigated by comparing the folding of wild-type **KIX** with the single point

mutants Y640F and R600M. The Y640F mutant disrupts a hydrogen bond involving the Tyr 640 OH and the backbone of V595 but still allows for the cation-pi interaction while the R600M mutant disrupts the cation-pi interaction. Both wild type **KIX** and Y640F exhibit properties expected of native like, globular proteins such as a single oligomerization state (monomer), cooperative thermal and urea-induced unfolding transitions, and a well-packed core. In contrast, the R600M mutant has properties reminiscent of a molten globule state, including a tendency to aggregate, noncooperative thermal unfolding transition, and a loosely packed core. Thus, the buried cation-pi interaction is critical for specifying the unique cooperatively folded structure of **KIX**.

L18 ANSWER 2 OF 8 MEDLINE on STN DUPLICATE 2
AN 2003544242 MEDLINE
DN PubMed ID: 14623102
TI Mutational analysis of the KIX domain of CBP reveals residues critical for SREBP binding.
AU Liu Ya-Ping; Chang Ching-Wen; Chang Kung-Yao
CS Institute of Biochemistry, National Chung-Hsing University, 250 Kuo-Kung Road, Taichung 402, Taiwan.
SO FEBS letters, (2003 Nov 20) 554 (3) 403-9.
Journal code: 0155157. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200312
ED Entered STN: 20031119
Last Updated on STN: 20031219
Entered Medline: 20031218
AB Structure-based mutagenesis was used to probe the binding surface for the activation domain of sterol-responsive element binding protein (SREBP) in the **KIX** domain of **CREB binding protein**. A set of conserved residues scattering in the alpha2 helix and the extended C-terminal region of alpha 3 helix in the **KIX** domain including two **arginines** previously characterized as a hot spot for cofactor-mediated methylation was shown to be crucial for SREBP-**KIX** interaction, and was not essential for phosphorylated KID recognition. Therefore, our results suggest the existence of a SREBP binding site formed by positively charged residues in the C-terminal part of the extended alpha 3 helix of the **KIX** domain distinct from the previously identified phosphorylated KID binding site.

L18 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 3
AN 2002617456 MEDLINE
DN PubMed ID: 12374746
TI Control of CBP co-activating activity by arginine methylation.
AU Chevillard-Briet Martine; Trouche Didier; Vandel Laurence
CS Laboratoire de Biologie Moleculaire Eucaryote, UMR 5099 CNRS, Institut de Biologie Cellulaire et Genetique, 118 Route de Narbonne, 31062 Toulouse cedex, France.
SO EMBO journal, (2002 Oct 15) 21 (20) 5457-66.
Journal code: 8208664. ISSN: 0261-4189.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200211
ED Entered STN: 20021011
Last Updated on STN: 20021214

Entered Medline: 20021126

AB The histone acetyltransferases **CREB binding protein** (**CBP**) and the related p300 protein function as key transcriptional co-activators in multiple pathways. In the case of transcriptional activation by nuclear receptors, ligand promotes the recruitment of co-activators of the p160 family, such as GRIP-1. Subsequently, the p160 co-activators recruit other co-activators via two activation domains, AD1 and AD2. AD1 binds CBP or p300, whereas AD2 has been shown to activate transcription through the recruitment of the **arginine** methyltransferase CARM1. Recently, the **KIX** domain of CBP has been shown to be methylated by CARM1 in vitro. Here, we report that another domain of CBP is specifically methylated by CARM1 on conserved **arginine** residues in vitro and in vivo. We also provide functional evidence that **arginine** residues methylated by CARM1 play a critical role in GRIP-1-dependent transcriptional activation and in hormone-induced gene activation. Altogether, our data provide strong evidence that **arginine** methylation represents an important mechanism for modulating co-activator transcriptional activity.

L18 ANSWER 4 OF 8 MEDLINE on STN DUPLICATE 4
AN 2001270011 MEDLINE
DN PubMed ID: 11073948
TI Increased affinity of c-Myb for **CREB-binding protein** (**CBP**) after **CBP**-induced acetylation.
AU Sano Y; Ishii S
CS Laborartory of Molecular Genetics, RIKEN Tsukuba Institute and the CREST (Core Research for Evolutional Science and Technology) Research Project of JST (Japan Science and Technology Corporation), 3-1-1 Koyadai, Tsukuba, Ibaraki 305-0074, Japan.
SO Journal of biological chemistry, (2001 Feb 2) 276 (5) 3674-82. Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200106
ED Entered STN: 20010625
Last Updated on STN: 20030105
Entered Medline: 20010621

AB The c-myb proto-oncogene product (c-Myb) is a sequence-specific DNA-binding protein that functions as a transcriptional activator. The transcriptional coactivator **CREB-binding protein** (**CBP**) binds via its **KIX** domain to the activation domain of c-Myb and mediates c-Myb-dependent transcriptional activation. CBP possesses intrinsic histone acetyltransferase activity, and can acetylate not only histones but also certain transcriptional factors such as GATA1 and p53. Here we demonstrate that the C/H2 domain of CBP, which is critical for the acetyltransferase activity, also directly interacts with the negative regulatory domain (NRD) of c-Myb. Consistent with this observation, CBP acetylated c-Myb in vitro at Lys(438) and Lys(441) within the NRD. In addition, CBP acetylated c-Myb in vivo not only at the sites found in this study but also at the p300-induced acetylation sites reported recently. Replacement of lysine by **arginine** at all of these sites dramatically decreased the trans-activating capacity of c-Myb. The results of transcriptional activation assays with c-Myb acetylation site mutants suggested that acetylation of c-Myb at each of these five sites synergistically enhances c-Myb activity. Mutations of these acetylation sites reduced the strength of the interaction between c-Myb and CBP. Thus, acetylation of c-Myb by CBP increases the trans-activating capacity of c-Myb by enhancing its association with CBP. These results demonstrate a novel molecular

mechanism of regulation of c-Myb activity.

L18 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 5
AN 2002004670 MEDLINE
DN PubMed ID: 11701890
TI A transcriptional switch mediated by cofactor methylation.
CM Comment in: Science. 2001 Dec 21;294(5551):2497-8. PubMed ID: 11752565
AU Xu W; Chen H; Du K; Asahara H; Tini M; Emerson B M; Montminy M; Evans R M
CS Gene Expression Laboratory, Department of Biological Chemistry, University of California Davis Cancer Center/Basic Science, Sacramento, CA 95817, USA.
NC 9R01DK57978 (NIDDK)
SO Science, (2001 Dec 21) 294 (5551) 2507-11.
Journal code: 0404511. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 20020102
Last Updated on STN: 20030105
Entered Medline: 20020226
AB We describe a molecular switch based on the controlled methylation of nucleosome and the transcriptional cofactors, the **CREB-binding proteins** (**CBP**)/p300. The **CBP**/p300 methylation site is localized to an **arginine** residue that is essential for stabilizing the structure of the **KIX** domain, which mediates **CREB** recruitment. Methylation of **KIX** by coactivator-associated **arginine** methyltransferase 1 (CARM1) blocks CREB activation by disabling the interaction between **KIX** and the kinase inducible domain (KID) of CREB. Thus, CARM1 functions as a corepressor in cyclic adenosine monophosphate signaling pathway via its methyltransferase activity while acting as a coactivator for nuclear hormones. These results provide strong in vivo and in vitro evidence that histone methylation plays a key role in hormone-induced gene activation and define cofactor methylation as a new regulatory mechanism in hormone signaling.

L18 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:7226 CAPLUS
DN 136:242280
TI Switching partners in a regulatory tango
AU Nishioka, Kenichi; Reinberg, Danny
CS Howard Hughes Med. Inst., Dep. Biochem., Robert Wood Johnson Med. Sch., Piscataway, NJ, 08854, USA
SO Science (Washington, DC, United States) (2001), 294(5551), 2497-2498
CODEN: SCIEAS; ISSN: 0036-8075
PB American Association for the Advancement of Science
DT Journal; General Review
LA English
AB A review on the issue of whether the cell contains enough cAMP response element-binding protein (CBP) and its paralog p300 to translate signal transduction into gene transcription at many promoter sites. Several lines of evidence suggest that both CBP and p300 are present in small amts. and thus are limited in most cells. Exptl. results indicate that the cellular pool of CBP/p300 is so small that any competition for these proteins has a demonstrable effect on cellular phenotype. A recent study by Xu et al. (2001) illustrates the mol. basis of the observed synergy between CBP/p300 and the enzyme CARM1 (coactivator associated **arginine** methyltransferase 1), and describes how CARM1 confers gene specificity upon CBP/p300. This study suggests that CBP/p300 and

CARM1 exist as a coactivator complex in which the histone acetyltransferase activity of CBP/p300 potentiates the histone H3 methyltransferase activity of CARM1, resulting in enhanced nuclear hormone receptor-dependent gene activation. Furthermore, the study showed that CARM1 methylates the **KIX** domain of **CBP**/p300, which interferes with the ability of **CBP**/p300 to interact with **CREB**'s KID motif, causing the loss of **CREB**-dependent gene activation.

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:282612 CAPLUS
DN 135:340116
TI Magnitude of the **CREB**-dependent transcriptional response is determined by the strength of the interaction between the kinase-inducible domain of **CREB** and the KIX domain of **CREB**-**binding protein**
AU Shaywitz, Adam J.; Dove, Simon L.; Kornhauser, Jon M.; Hochschild, Ann; Greenberg, Michael E.
CS Program in Biological and Biomedical Sciences, Harvard Medical School, Children's Hospital, Boston, MA, 02115, USA
SO Molecular and Cellular Biology (2000), 20(24), 9409-9422
CODEN: MCEBD4; ISSN: 0270-7306
PB American Society for Microbiology
DT Journal
LA English
AB The activity of the transcription factor CREB is regulated by extracellular stimuli that result in its phosphorylation at a critical serine residue, Ser133. Phosphorylation of Ser133 is believed to promote **CREB**-dependent transcription by allowing **CREB** to interact with the transcriptional coactivator **CREB**-**binding protein** (**CBP**). Previous studies have established that the domain encompassing Ser133 on **CREB**, known as the kinase-inducible domain (KID), interacts specifically with a short domain in **CBP** termed the KIX domain and that this interaction depends on the phosphorylation of Ser133. In this study, the authors adapted a recently described Escherichia coli-based two-hybrid system for the examination of phosphorylation-dependent protein-protein interactions, and they used this system to study the kinase-induced interaction between the KID and the KIX domain. The authors identified residues of the KID and the KIX domain that are critical for their interaction as well as two pairs of oppositely charged residues that apparently interact at the KID-KIX interface. The authors then isolated a mutant form of the KIX domain that interacts more tightly with wild-type and mutant forms of the KID than does the wild-type KIX domain. The authors show that in the context of full-length **CBP**, the corresponding amino acid substitution resulted in an enhanced ability of **CBP** to stimulate **CREB**-dependent transcription in mammalian cells. Conversely, an amino acid substitution in the KIX domain that weakens its interaction with the KID resulted in a decreased ability of full-length **CBP** to stimulate **CREB**-dependent transcription. These findings demonstrate that the magnitude of CREB-dependent transcription in mammalian cells depends on the strength of the KID-KIX interaction and suggest that the level of transcription induced by coactivator-dependent transcriptional activators can be specified by the strength of the activator-coactivator interaction.

RE.CNT 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 8 OF 8 MEDLINE on STN DUPLICATE 6
AN 96140437 MEDLINE

DN PubMed ID: 8552098
TI Phosphorylation of **CREB** at Ser-133 induces complex formation with **CREB-binding protein** via a direct mechanism.
AU Parker D; Ferreri K; Nakajima T; LaMorte V J; Evans R; Koerber S C; Hoeger C; Montminy M R
CS Clayton Foundation Laboratories for Peptide Biology, Salk Institute, La Jolla, California 92037, USA.
NC CA54418 (NCI)
GM37828 (NIGMS)
SO Molecular and cellular biology, (1996 Feb) 16 (2) 694-703.
Journal code: 8109087. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199602
ED Entered STN: 19960306
Last Updated on STN: 19960306
Entered Medline: 19960221
AB We have characterized a phosphoserine binding domain in the coactivator **CREB-binding protein** (**CBP**) which interacts with the protein kinase A-phosphorylated, and hence activated, form of the cyclic AMP-responsive factor **CREB**. The CREB binding domain, referred to as **KIX**, is alpha helical and binds to an unstructured kinase-inducible domain in CREB following phosphorylation of CREB at Ser-133. Phospho-Ser-133 forms direct contacts with residues in **KIX**, and these contacts are further stabilized by hydrophobic residues in the kinase-inducible domain which flank phospho-Ser-133. Like the src homology 2 (SH2) domains which bind phosphotyrosine-containing peptides, phosphoserine 133 appears to coordinate with a single **arginine** residue (Arg-**600**) in **KIX** which is conserved in the CBP-related protein P300. Since mutagenesis of Arg-**600** to Gln severely reduces **CREB-CBP** complex formation, our results demonstrate that, as in the case of tyrosine kinase pathways, signal transduction through serine/threonine kinase pathways may also require protein interaction motifs which are capable of recognizing phosphorylated amino acids.